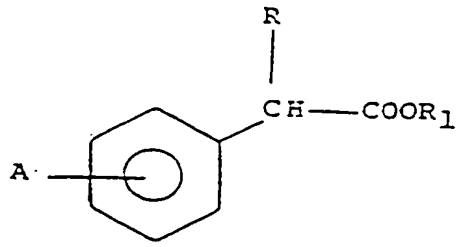
A PROCESS FOR THE PREPARATION OF ALPHA-ARYLALKANOIC ACIDS

The present invention relates to a process for the preparation of meta or para-substituted α-arylalkanoic acids.

More particularly, the invention relates to a process for the preparation of compounds of formula (I)

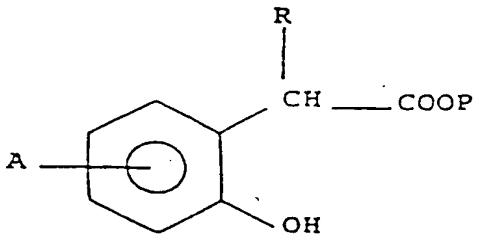


(I)

wherein:

R is hydrogen, C_1-C_6 alkyl; R_1 is hydrogen, straight or branched C_1-C_6 alkyl, phenyl, p-nitrophenyl, a cation of an alkali or alkaline-earth metal cation or of a pharmaceutically acceptable ammonium salt; A is C_1-C_4 alkyl, aryl, aryloxy, arylcarbonyl, 2-, 3- or 4-pyridocarbonyl, aryl optionally substituted with one or more alkyl, hydroxy, amino, cyano, nitro, alkoxy, haloalkyl, haloalkoxy; A is at the meta or para positions;

starting from compounds of formula (II)



(II)

(II)

in which P is straight or branched C_1-C_6 alkyl, phenyl, p-nitrophenyl.

Different strategies are at present used for removing the phenolic hydroxyl of arylalkanoic acids derivatives, based on the derivatization and subsequent elimination of the derivative by reduction, but in most cases such procedures suffer from drawbacks such as high-cost reagents or lack of selectivity.

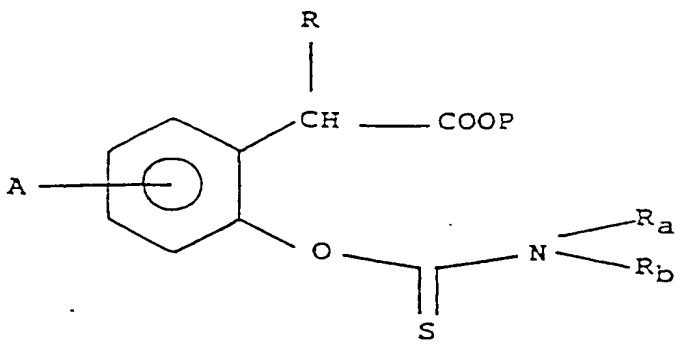
British Patent 2025397 (Chinoin), discloses the use of various derivatives of the phenolic hydroxyl, such as phenylaminocarbonyl, 1-phenyl-5-tetrazolyl, 2-benzoxazolyl, $-SO_2OMe$, and the reduction of the derivative with hydrogen on Pd/C catalyst.

WO 98/05632 application, in the Applicant's name, discloses the use of perfluoroalkanesulfonates, in particular trifluoromesylate, followed by reduction with formic acid and triethylamine in the presence of palladium acetate / triphenylphosphine complex.

It has now been found a process for the preparation of arylpropionic acids starting from the corresponding α-hydroxylated derivatives, using inexpensive reagents and keeping intact any reducible groups, such as esters or ketones, present on the side chains of the starting molecules.

According to the process of the invention, the compounds of formula (I) are prepared through the following steps:

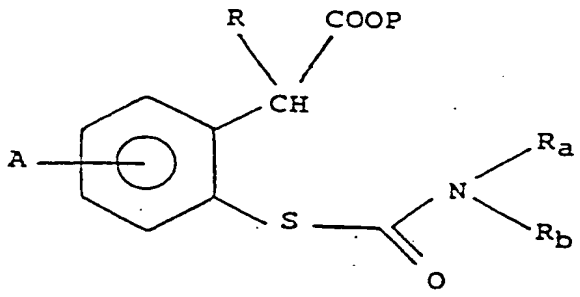
a) transformation of compounds of formula (II) into compounds of formula (III):



(III)

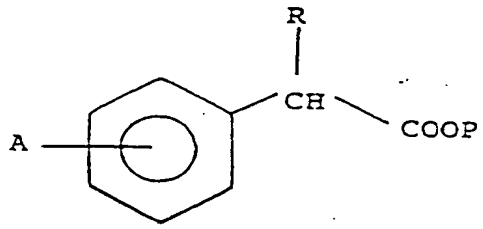
wherein R_a and R_b are C_1-C_6 alkyl, preferably methyl;

b) thermal rearrangement of compound (III) to give (IIIb)



(IIIb)

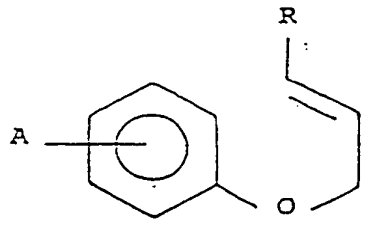
c) catalytic hydrogenation of (IIIb) to give (IIIc)



(IIIc)

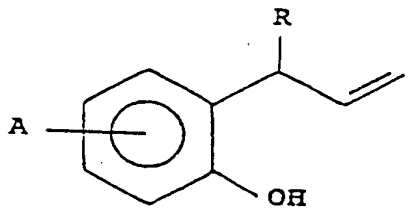
d) transformation of (IIIc) into (I).

The compounds of formula (II) can be prepared as described in WO 98/05623. Briefly, starting from arylolefins of formula (IV)



(IV)

wherein A and R have the same meanings as defined above, by Claisen rearrangement, compound (V) is obtained

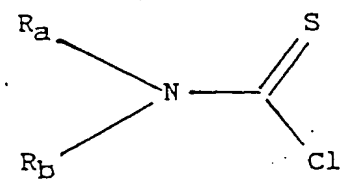


(V)

which can be subsequently subjected to oxidative cleavage, for example by ozonolysis or with potassium permanganate in phase transfer conditions, thus yielding the corresponding carboxylic acid product. The latter can be transformed into compound (II) by esterification with a suitable alcohol.

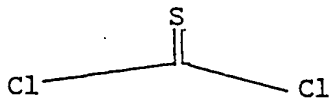
Step a) can be carried out in two ways.

In the first case, compound of formula (II) is reacted with

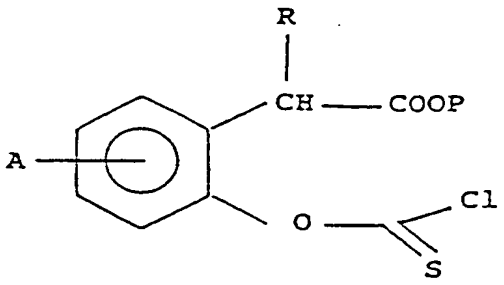


wherein R_a and R_b are as defined above, in the presence of an inorganic base such as an alkali or alkaline-earth carbonate, or an organic one, such as triethylamine or pyridine.

Alternatively, compound of formula (II) is reacted first with thiophosgene,



to obtain compound (IIIa)



(IIIa)

which is subsequently reacted with HNR_aR_b in which R_a and R_b are as defined above.

The conversion of the phenol in O-aryl-dialkylthiocarbamate by reaction with R_bR_aNCSCl, and the subsequent thermal rearrangement (step b) of the O-aryl dialkylthiocarbamate to give compound (IIIb), are described in Newman and Karnes, "The conversion of phenols", J. Org. Chemistry, Vol. 31, 1966, 3980-3982.

On the other hand, as for the preparation of the O-aryl-dialkylthiocarbamate by reacting the phenol with

thiophosgene and subsequently the resulting product with amine R_aR_bNH, the method reported in Can. J. Chem., 38, 2042-52 (1960) can be followed.

In step c), the catalytic hydrogenation of S-aryl-dialkylthiocarbamate (IIIb) to give (IIIc) can be carried out with Ni-Raney as catalyst.

Compound (IIIc) is easily converted to (I) through conventional procedures for the hydrolysis of the ester group and optional subsequent reesterification or salification of the carboxylic group.

The process of the invention proved to be particularly advantageous when group A in general formula (I) is an optionally substituted aroyl group, in that the carbonyl function is preserved during the reduction of the thiocarbamoyl derivative. For example, when A is benzoyl, no reduction of the ketone under the used experimental conditions is observed. Furthermore, as already mentioned, the process of the invention is based on the use of low cost reagents, provides good yields, requires no purifications of the intermediates and has a low environmental impact.

The following examples illustrate the invention in greater detail.

Example 1

Preparation of 2-(3'-benzoyl-2'-hydroxyphenyl)-propionic acid methyl ester (2)

A solution of 2-(3'-benzoyl-2'-acetoxyphenyl)propionic acid (1) (6.2 g) in methanol (35 ml) was added with concentrated H_2SO_4 (0.3 ml). The mixture was stirred at room temperature for 15 hours until disappearance (1) and of the reaction intermediates. The solvent was evaporated off under vacuum and the residue

was dissolved in ethyl acetate (30 ml) and washed with water. The organic layer was treated with a NaOH solution (100 ml), and the basic phase was acidified with 4N HCl and extracted with ethyl acetate (2 x 25 ml). The collected organic layers were washed with brine, dried over Na_2SO_4 and evaporated under vacuum. The crude product (4.3 g) was dissolved in isopropyl ether (5 ml) and the slightly yellow precipitate was filtered. n-Hexane (25 ml) was added to the residue and the mixture was stirred overnight. After filtration, 3.2 g of (2) were obtained (0.11 mol; 70% yield starting from 4) as a whitish solid (melting point 108-111°C).

TLC (CH_2Cl_2/MeOH 9:1 Rf = 0.45)

Elementary analysis calculated for $C_{17}H_{16}O_3$: C-71.81, H-5.67.

Found: C-71.16, H-5.63.

^{1}H-NMR ($CDCl_3$) d 8.4 (s, OH, 1H); 7.85-7.3 (m, 7H); 7.0 (d, 1H, J = 7 Hz); 3.95 (q, 1H, 8 Hz); 3.8 (s, 3H); 1.6 (d, 3H, J = 8 Hz).

Example 2

Preparation of 2-(3'-benzoyl-2'-O-dimethylthiocarbamoylphenyl)-propionic acid methyl ester (3)

A solution of (2) (3.2 g, 0.011 mol) in acetone (25 ml) was added with potassium carbonate (1.65 g, 0.012 mol) and the mixture was stirred at room temperature for 15 min. A solution of N,N-dimetilcarbamoyl chloride (1.51 g, 0.012 mol) in acetone (5 ml) was added drop by drop to the refluxed mixture for 2 hours. After cooling at room temperature, the precipitated inorganic salts were filtered off and the solvent was evaporated under vacuum. The residue was dissolved in ethyl acetate (25 ml) and washed with water (2 x 10 ml) and brine (2 x 10

ml). The organic phase was dried over Na_2SO_4 and evaporated under vacuum, to obtain 3.45 g of (3) as a dark oil sufficiently pure to be used in the subsequent step.

TLC (n-hexane/EtOAc 8:2) Rf = 0.25

Elementary analysis calculated for $C_{20}H_{22}NO_4S$: C-64.49, H-5.95, N-3.76, S-8.61.

Found: C-64.17, H-5.92, N-3.82, S-8.60.

^{1}H-NMR ($CDCl_3$) d 7.95-7.8 (m, 4H); 7.6-7.4 (m, 3H); 7.2 (d, 1H, J = 7 Hz); 3.9 (q, 1H, J = 8 Hz); 3.7 (s, 3H); 3.6 (s, 3H); 3.4 (s, 3H) 1.6 (d, 3H, J = 8 Hz).

Example 3

Preparation of 2-(3'-benzoyl-2'-S-dimethylthiocarbamoylphenyl)propionic acid methyl ester (4)

Compound (3) (3.45 g) was heated in a flask at T = 210°C (temperature of the outer oil bath) for 2 hours under stirring. After cooling at room temperature and evaporation under vacuum, 3.45 g of (4) were obtained (0.0054 mol) sufficiently pure to be used without further purifications.

TLC (n-hexane/ethyl acetate 8:2 Rf = 0.2).

Elementary analysis calculated for $C_{20}H_{22}NO_4S$: C-64.49, H-5.95, N-3.76, S-8.61.

Found: C-64.17, H-5.92, N-3.82, S-8.60.

^{1}H-NMR ($CDCl_3$) d 7.9-7.8 (m, 3H); 7.7-7.3 (m, 5H); 4.4 (q, 1H, J = 8 Hz); 3.65 (s, 3H); 3.2-2.9 (d broad, 6H); 1.6 (d, 3H, J = 8 Hz).

Example 4

Preparation of 2-(3'-benzoylphenyl)-propionic acid methyl ester (5)

Acetone (50 ml) was added to Ni-Raney (50% in water, 20 ml) and the water/acetone mixture was removed.

The treatment was repeated 3 times. Subsequently the catalyst was suspended in acetone (30 ml) and refluxed for 30 hours.

A solution of (4) (3.45 g) in acetone (4 ml) was added drop by drop and the mixture was refluxed overnight. After cooling at room temperature, the catalyst was filtered off and washed with acetone (10 ml). The filtrate was evaporated under vacuum, to obtain 2.4 g of (5) as a slightly brown oil.

TLC (n-hexane/ethyl acetate 9:1 Rf = 0.7)

Elementary analysis calculated for $C_{17}H_{16}O_3$: C-76.10, H-6.01.

Found: C-75.99, H-6.03.

^{1}H-NMR ($CDCl_3$) d 7.9-7.4 (m, 8H); 3.8 (q, 1H, J = 8 Hz); 3.65 (s, 3H); 1.6 (d, 3H, J = 8 Hz)

Example 5

Preparation of 2-(3'-benzoylphenyl)propionic acid (6)

The solution of (5) (2.4 g, 0.009 mol) in methyl alcohol (25 ml) was added with 1N NaOH (13.5 ml) and the mixture was left under stirring for 8 hours at room temperature. After evaporating the solvent, the residue was diluted with water and 5% monobasic sodium phosphate was added drop by drop to the mixture to adjust pH to 5. The aqueous layer was then extracted with methyl acetate (2 x 100 ml). The collected organic extracts were dried over Na_2SO_4 and evaporated under vacuum, then crystallized from a benzene/petroleum ether 6:20 mixture to obtain 2.05 g of (6) (0.0081 mol; yield 90%) as a white solid (melting point 92-92°C) following crystallization.

TLC ($CHCl_3/CH_3OH$ 95:5) Rf = 0.2

Elementary analysis calculated for $C_{16}H_{14}O_3$: C-75.57, H-5.55.

Found: C-75.19, H-5.53.

^{1}H-NMR ($CDCl_3$) d 7.91-7.75 (d, 3H), 7.74-7.51 (m, 2H), 7.50-7.35 (m, 4H), 3.85 (q, 1H, J = 10 Hz), 1.58 (d, 3H, J = 10 Hz).